REMARKS

Claims 1-33 are pending in the above application. Claims 25-33 are withdrawn as directed to a non-elected invention. Claims 14-15 are canceled herein without prejudice. Claims 1, 3, 4, 5, 21 and 23 are amended herein for clarity to more particularly define the invention. The specification is amended herein to complete a citation to a non-patent reference, as requested by the Examiner. Support for these amendments is found in the language of the original claims and throughout the specification as set forth below. No new matter is added by these amendments and applicants respectfully request their entry and examination. In light of these amendments and the following remarks, applicants respectfully request reconsideration of this application and allowance of the pending claims to issue.

I. Information Disclosure Statement

The Office Action states that copies of the non-patent literature documents submitted with the September 18, 2002 Information Disclosure Statement (IDS) were not received and that these documents must be submitted if they are to be considered by the Examiner.

Applicants enclose a copy of each of the non-patent documents listed on the PTO Form 1449 submitted to the USPTO on September 13, 2002. Also enclosed is a copy of the postcard accompanying the September 2002 submission that lists 28 references enclosed with the IDS documents. Receipt of these documents is acknowledeged by the USPTO as evidenced by the OIPE date stamp showing the date of September 18, 2002 (copy enclosed). Thus, although these documents were submitted to the USPTO with the IDS filing on September 13, 2002, they appear to be missing from this file and applicants provide duplicate copies of each. Applicants respectfully request consideration of each of these references and provide an unmarked copy of the originally filed PTO Form 1449 for the Examiner to initial upon consideration of these documents. Applicants request that the Examiner contact the undersigned directly if any further information is required.

A supplemental Information Disclosure Statement is also included herewith for the Examiner's consideration.

II. Specification

The Office Action states that the specification is objected to due to an incomplete citation of a reference by Sockman et al. on page 11, line 24.

The specification is amended herein to complete the Sockman et al. citation, thereby mooting this objection and applicants respectfully request its withdrawal.

III. Claim objections

The Office Action states the claims 2-13, 16-17, 19, 21 and 23 are objected to because of the inconsistent spelling of the word "labeled" (and "labelled") in the claims.

Claims 2, 3 and 21 are amended herein to recited "labelled," thereby maintaining consistency throughout the claims and rendering this objection moot. Applicants respectfully request its withdrawal.

IV. Rejection under 35 U.S.C. § 112, first paragraph

The Office Action states that claims 1-24 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for determining active PAI-1 in biological samples other than serum, plasma, platelets and platelet releasates.

Applicants maintain that the examples taught in the specification soundly predict and can be extended to all biological fluids. However, in order to expedite prosecution, claim 1 is amended herein to specify that the biological fluids are selected from the group consisting of whole blood, platelet releasates, platelet plasma, plasma, serum, and a combination of same.

Support for this amendment can be found throughout the specification including, e.g., on page 6, line 32 and elsewhere. Thus, this rejection has been overcome and applicants respectfully request its withdrawal.

IV. Rejection under 35 U.S.C. § 112, second paragraph

A. The Office Action states that claim 1 is allegedly indefinite as being incomplete for omitting essential steps. The Office Action states that the omitted step is a correlation step describing how the measurement of PAI-1/multimeric vitronectin relates back to the method recited in the preamble (determination of active PAI-1).

Claim 1 is amended herein to include the correlation step, thereby overcoming this rejection and applicants respectfully request its withdrawal.

B. The Office Action states that claim 5 is allegedly indefinite as lacking antecedent basis for "the PAI-1/multimeric vitronectin/first antibody/second antibody complex."

Claims 4 and 5 are amended herein to address this antecedent basis issue, thereby overcoming this rejection and applicants respectfully request the withdrawal of this rejection.

C. The Office Action states that claim 23 is allegedly indefinite as lacking antecedent basis for "the second antibody" in line 1.

Claim 23 is amended herein to depend from claim 3, thereby addressing this issue and overcoming this rejection and applicants respectfully request its withdrawal.

D. The Office Action states that claim 23 is also allegedly indefinite in the recitation of biotin/avidin.

Claim 23 is amended herein to recite biotin and avidin, thereby addressing this indefiniteness issue and overcoming this rejection. Thus, applicants respectfully request its withdrawal.

VI. Rejection under 35 U.S.C. § 102(b)

A. The Office Action states that claim 1 is rejected as allegedly anticipated by Lawrence et al. (*Journal of Biological Chemistry* (1997) **272**:7676-7680), or alternatively by Lawrence et al. (WO 97/39028). Specifically, the Office Action states that Lawrence et al. teaches a method for determining active PAI-1 in a biological fluid and in particular, Lawrence at al. teaches measuring the amount of PAI-1 bound to vitronectin in a sample of biological fluid. The Examiner contends that the PAI-1 measured is active and that the biological fluid is the liquid sample in the microtiter plates in which the reaction takes place. The Office Action further states that Lawrence et al. teaches measuring the amount of PAI-1 bound to both monomeric vitronectin and to urea-purified vitronectin, which is multimeric.

Applicants respectfully disagree that claim 1 is anticipated by Lawrence et al. Specifically, claim 1 is directed to a method for determining active PAI-1 by measuring the amount of active PAI-1/multimeric vitronectin complex in a biological fluid sample and then utilizing that measurement to determine the amount of active PAI-1 in the biological fluid. In contrast, Lawrence et al. states that active PAI-1 binds to both multimeric and monomeric vitronectin. Applicants submit that Lawrence et al. actually teaches against the method of claim 1, as Lawrence et al. teaches the need to assay both the PAI-1 bound to multimeric vitronectin and the PAI-1 bound to monomeric vitronectin to determine the amount of PAI-1 in any given biological fluid. Although Lawrence et al. may appear to teach that active PAI-1 binds to multimeric vitronectin, Lawrence et al. does not teach determining the amount of active PAI-1 in a biological fluid by correlating it to the amount of PAI-1 multimeric vitronectin complex in the sample. From the teachings of Lawrence et al., if one wanted to determine the active PAI-1 in a biological fluid, one would have to assay both mono- and multimeric vitronectin bound PAI-1.

Furthermore, according to the teachings of Lawrence et al., the vitronectin is added to the assay and is not the vitronectin that is already contained within the sample of biological fluid. Lawrence et al. describes the use of vitronectin bound to a plate (i.e., a vitronectin that is foreign to the sample) as a solid phase, and then the measurement of PAI-1 bound to that immobilized vitronectin. Thus Lawrence et al. does not measure the amount of active PAI-1/multimeric vitronectin complex in the sample, as set forth in claim 1. Rather, Lawrence et al. teaches the measurement of the amount of active PAI-1 that binds to a separately provided, foreign vitronectin that is already bound to the assay plate.

For at least the reasons set forth above, claim 1 as presented herein is not anticipated by Lawrence et al. and applicants respectfully request the withdrawal of this rejection.

B. The Office Action states that claims 1-2, 4, 6-8, 10, 14 and 23-24 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Preissner et al. Specifically, the Office Action states that Preissner et al. teaches a method comprising measuring the amount of PAI-1/multimeric vitronectin complex in a biological fluid sample. The Examiner argues that although Preissner et al. does not specifically recite that active PAI-1 is determined, this would inherently be the case since the method measures the PAI-1 that is bound to vitronectin, which is the active PAI-1.

Applicants respectfully disagree with this rejection and assert that claims 1-2, 4, 6-8, 10, 14 and 23-24 are not anticipated by Preissner et al. Specifically, Preissner et al. measures PAI-1 bound to vitronectin in general, not to multimeric vitronectin alone. Thus, since monomeric vitronectin binds non-active PAI-1, the method in Preissner et al. would pick up "non-active" PAI-1. Also please see page 6, lines 17-26 of the present patent application, which further distinguishes Preissner et al. over the invention at hand. Specifically, the method taught in Preissner et al. appears flawed in that it offers contradictory results when repeated, for example,

by Lang et al., (1996), J. Biol. Chem., v. 271, pp. 2754-2761, and Nordenhem et al (1997), Scand. J. Clin. Inest., v. 57, p. 453.

Furthermore, the claimed invention has another specific and significant advantage over the methods of both Lawrence et al. and Preissner et al. in that the amount of vitronectin bound to PAI-1 is known to be less than 0.1% of the total vitronectin in the serum. Therefore, the assays described in Lawrence et al. and Preissner et al. would require binding an excess amount of antibody to all of the vitronectin in the serum, meaning much larger amounts of antibody are required to perform the assays described in Lawrence et al. and Preissner et al. as compared to the assay described in the present invention and claimed in the present claims. By measuring the amount of PAI-1/multimeric vitronectin complex instead of measuring all of the vitronectin in the sample, one reduces costs and eliminates steps. Both a reduction of costs and elimination of steps are achieved by the method claimed.

Claim 14 is canceled herein without prejudice, thereby mooting this rejection as it pertains to this claim. All of the remaining claims cited in this rejection depend, either directly or indirectly, from claim 1, which is distinguished from the teachings of Preissner et al., as set forth above. Thus, neither claim 1 nor any of these dependent claims are anticipated by Preissner et al. and applicants respectfully request the withdrawal of this rejection.

VII. Rejection under 35 U.S.C. § 103

The Office Action states that claims 3, 5, 9 and 11 are rejected under 35 U.S.C. § 103 as allegedly obvious in view of Preissner et al. in view of Harlow et el. Specifically, the Office Action states that it would have been obvious to one of ordinary skill in the art to employ the anti-vitronectin antibody as the solid phase antibody and the anti-PAI-1 antibody as the labeled antibody in the method of Preissner et al. because Harlow et al. teaches that both combinations should be tried to determine which is best in a two-antibody sandwich assay, such as that of Preissner et al.

B. The Office Action states that claim 12 is rejected under 35 U.S.C. § 103 as allegedly obvious over Preissner et al. in view of Forrest et al. Specifically, the Office Action states that it would have been obvious to label the first antibody with avidin or biotin for immobilizing to the solid support in the method of Preissner et al. because Forrest et al. teaches that such specific binding proteins constitute a rapid, high affinity binding system for immobilizing antibodies to solid supports.

C. The Office Action states that claim 13 is rejected under 35 U.S.C. § 103 as allegedly obvious over Preissner et al. in view of Harlow et al. and Forrest et al. Specifically, the Office Action states that it would have been obvious to label the first antibody with avidin or biotin for immobilizing to the solid support in the method of Preissner et al. because Forrest et al. teaches that such specific binding proteins constitute a rapid, high affinity binding system for immobilizing antibodies to solid supports and that it would have been further obvious to contact the sample with the first and second antibodies and then to contact the mixture with the solid support with bound avidin or biotin because Forrest et al. teaches that this preferable.

D. The Office Action states that claim 15 is rejected under 35 U.S.C. § 103 as allegedly obvious over Preissner et al. in view of Sigurdardottir et al. Specifically, the Office Action states that it would have been obvious to employ the method of Preissner et al. with plasma samples because Sigurdardottir et al. teaches that PAI-1 may be a marker of thrombotic disease or recurrent myocardial infarction.

E. The Office Action states that claims 16-18 are rejected under 35 U.S.C. § 103 as allegedly obvious over Preissner et al. in view of Harlow et al. and Ehrlich et al. Specifically, the Office Action states that it would have been obvious to directly rather than indirectly label the second antibody with the peroxidase label in the method of Preissner et al. and Harlow et al. because Ehrlich et al. teaches that indirect and direct labels are both suitable for sandwich

immunoassays, which is the assay format used by Preissner et al. and Harlow et al.

F. The Office Action states that claims 19-22 are rejected under 35 U.S.C. § 103 as allegedly obvious over Preissner et al. in view of Harlow et al. and Valenzuela et al. Specifically, the Office Action states that it would have been obvious to employ a fluorophore such as rhodamine or a luminescent material such as acridinium ester as taught by Velenzuela et al. in the method of Harlow et al. because Valenzuela et al. teaches that such compounds are commonly known antibody labels for use in immunoassays.

Claim 15 is canceled herein without prejudice, thereby mooting this rejection as it pertains to this claim. All of the 35 U.S.C. § 103 rejections cited herein are based on Preissner et al. as a primary reference. As noted above, the claimed invention is distinguished from Preissner et al. because Preissner et al. discloses the measurement of PAI-1 bound to vitronectin in general, not to multimeric vitronectin alone and therefore does not teach or suggest a method of determining active PAI-1 in a biological fluid by measuring the amount of active PAI-1/multimeric vitronectin complex in a sample of the biological fluid. Thus, the disclosure of Preissner et al. provides no motivation or reasonable expectation of success in carrying out the method of the present invention, either alone or in combination with any of the secondary references cited herein. Nothing in Preissner et al., either alone or in combination with any of the other teachings presented above, would have provided the ordinary artisan with motivation to measure the amount of active PAI-1/multimeric vitronectin since Preissner et al. only teaches measuring the amount of PAI-1 bound to all vitronectin (and not simply multimeric vitronectin). As discussed above, the measuring of PAI-1 bound to multimeric vitronectin alone (rather than to all vitronectin) offers significant advantages, and is taught against in Preissner et al. Thus, claims 3, 5, 9, 11-13 and 15-22 would not have been obvious to one of ordinary skill in the art at the time this invention was made on the basis of these teachings and applicants respectfully request the withdrawal of this rejection.

For the reasons set forth above, applicants believe that all of the pending rejections have been adequately addressed and that the present claims are in condition for allowance, which action is respectfully requested. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of this application to issue.

A check in the amount of $410.00 ($225.00 as the fee for a two month extension of time for a small entity and $180.00 as fee for the supplemental IDS) is enclosed. This amount is believed to be correct. However, the Commissioner is authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-0220.

Respectfully submitted,

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